REMARKS

The Invention

The present invention is directed to compositions capable of inducing an immune response to cytotoxic T cell epitopes of a full length viral protein in a mammal. The composition comprises an amount of *Bacillus anthracis* anthrax PA ("PA") and a full length viral protein bound to an APABP ("APABP") sufficient to elicit an MHC class I-mediated cytotoxic T lymphocyte cell ("CTL") immune response specific for the viral protein. The APABP comprises at least the first 250 amino acid residues of the lethal factor of *Bacillus anthracis* and less than all of the amino acid residues of the lethal factor. In some embodiments, the molar ratio of PA to the full length viral protein bound to the APABP is greater than one.

Status of the Claims

After entry of this amendment, claims 1-6 and 30-31 are pending in the application. Claim 29 has been canceled without prejudice to future prosecution. Claims 1 and 30 have been amended. Support for these amendments is found in the specification at, *e.g.*, page 2, line 17 to page 3, line 11 and page 9, line 31. Thus, no new matter is added by these amendments.

Claims 1-6, 29, and 31 are rejected under 35 U.S.C. § 103(a) and claims 29 and 30 are rejected under 35 U.S.C. § 112, first paragraph. These rejections are addressed in detail below in the order presented by the Examiner.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 29, and 30 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

1. Claim 29

To expedite prosecution, claim 29 has been canceled without prejudice to future prosecution. Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

2. Claim 30

In accordance with the Examiner's suggestion and to expedite prosecution, claim 30 has been amended to recite "herpes simplex virus protein NS-5b." Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103

Claims 1-6, 29, and 31 are rejected under 35 U.S.C. § 103 as allegedly unpatentable over WO 94/18332 ("Leppla *et al.*") in view of WO 95/03414 ("Noteborn *et al.*"). In making the rejection, the Examiner acknowledges that Leppla *et al.* do not teach a full length viral protein bound to APABP, but alleges that in view of the teachings of Noteborn *et al.* it would have been obvious generate such a fusion protein. The rejection further alleges that the intended use of the claimed compositions carries no patentable weight. Finally, the rejection alleges that Leppla *et al.* discloses the functional dosage recited in the claims. Applicants respectfully traverse each of the aspects of this rejection.

As previously explained, to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure (*see*, MPEP, § 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). As previously noted, the

proposed modification cannot render the prior art unsatisfactory for its intended purposes (*see*, MPEP §2143.01, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)).

Moreover, as previously noted, all of the claim limitations must be considered and given weight when evaluating claims for obviousness (*see, e.g.*, MPEP § 2143.03) and a functional limitation in a claim must be evaluated and considered just like any other limitation (*see, e.g.*, MPEP § 2173.05(g)).

The present invention is directed to compositions capable of inducing an immune response to cytotoxic T cell epitopes of a full length ***viral*** protein in a mammal. The claims require that the compositions comprise *Bacillus anthracis* anthrax PA and full length viral protein bound to an APABP in an amount sufficient to elicit a cytotoxic T lymphocyte cell ("CTL") response, *i.e.*, an MHC class I-mediated immune response, specific for the viral protein. Thus, the claims require: (1) a structural element, *i.e.*, a full length viral protein bound to an APABP; and (2) a functional element, *i.e.*, "an amount sufficient to elicit an MHC class I-mediated cytotoxic T lymphocyte response specific for the administered viral protein." Both of these elements are relevant to the patentability of the presently claimed compositions and must be given weight when evaluating the claims for obviousness under 35 U.S.C. § 103.

As discussed in detail below, the required elements of the present claims are not disclosed or suggested by Leppla *et al.* in view of Noteborn *et al.* Moreover, one of skill in the art would have no motivation to combine the disclosure of Leppla *et al.* with the disclosure of Noteborn *et al.* to generate the presently claimed compositions. Even if one of skill in the art were to combine the disclosure of Leppla *et al.*, and Noteborn *et al.* there would be no reasonable expectation of success in generating the presently claimed vaccine compositions.

As Dr. Leppla has clarified in his Declaration, it is well known in the art that immune responses are based on two distinct pathways: MHC class I and MHC class II (*see*, Declaration ¶6 and Exhibit B). The MHC class I pathway is associated with endogenously synthesized antigens and the MHC class II pathway is associated with exogenously synthesized and endocytosed antigens (*see*, Declaration ¶6). ***CTL*** responses specific for a particular endogenous antigen are produced following presentation by MHC ***class I*** molecules to CTLs and

antibodies specific for a particular exogenous antigen are produced following presentation of epitopes by MHC ***class II*** molecules to helper T cells. (*see*, Declaration ¶6)

Dr. Leppla explains that the present invention is based on the surprising discovery that the anthrax toxin system can be used to deliver full length viral proteins as ***exogenous*** antigens to the cell cytosol for processing and presentation by MHC class I molecules to cytotoxic T lymphocyte cells (CTLs) to elicit a cytotoxic T lymphocyte immune response specific for the viral protein (*see*, Declaration ¶3). More particularly, the present application provides the first evidence that a bacterial toxin system (anthrax toxin) can be used to exogenously introduce a ***full length*** viral protein into the cytosol for processing via the MHC ***class I*** pathway and presentation by MHC class I molecules to CTLs (*see* Declaration ¶7 and ¶12 and the specification at page 3, lines 7-11). The use of full length viral protein has the advantage of providing multiple epitopes that are recognized by more than one MHC class I allele (*see*, Declaration ¶3). The present inventors are therefore the first to show that a full length viral protein, fused to LF and translocated into a cell by anthrax toxin, is processed by the cytosolic MHC ***class I*** pathway and presented by MHC class I molecules to CTLs (*see*, *id.*).

Leppla et al. and Noteborn et al. alone or in combination do not contain all of the required elements of the presently claimed compositions

Leppla *et al.* is cited as teaching compositions containing anthrax PA and fusion protein containing the PA binding domain of LF and a full length protein. As explained previously and further clarified by Dr. Leppla, Leppla *et al.* generically discloses compositions comprising *B. anthracis* anthrax PA and peptides or protein fragments bound to an APABP and methods of using the compositions to deliver an activity to a cell (*e.g.*, a toxic activity) (*see*, Declaration ¶7). For example, Leppla *et al.* teaches methods for cellular delivery of small fragments of proteins or peptide epitopes, rather than full viral length proteins, using anthrax toxins comprising PA and a LF-viral protein fusion proteins (*see*, Declaration ¶8). The present invention represents a separately patentable subgenus of the compositions described in Leppla *et al.* In contrast to Leppla *et al.*, the presently claimed invention is a vaccine composition using a

bacterial toxin (*e.g.*, an APABP) to exogenously introduce a ***full length viral*** protein into the cytosol of a target cell for processing via the MHC ***class I*** pathway and presentation by MHC class I molecules to CTLs (*see*, Declaration ¶7).

At page 3, ¶7, lines 9-10 of the Office Action, the Examiner asserts that processed PA is created when the anthrax PA is administered *in vivo* and appears to equate cleavage of PA with processing an antigen into epitopes. However, as Dr. Leppla clarifies, anthrax toxin is a binary bacterial toxin comprising two proteins: LF and PA (*see*, Declaration ¶8). PA binds to the cellular receptor and is cleaved, revealing an LF binding site (*see*, Declaration ¶8). LF then binds to PA, forming anthrax toxin which is translocated into the cell (*see*, Declaration ¶8). Cleavage of PA reveals its LF binding site and does ***not*** generate epitopes of PA for presentation by MHC class I molecules to CTLs (*see*, Declaration ¶8). Thus, Leppla *et al.* does not teach the use of anthrax toxin fusion proteins: (1) comprising a ***full-length protein*** (*i.e.*, a viral protein) bound to a APABP; and (2) an amount sufficient to elicit an MHC class I-mediated CTL response specific for the viral protein. Therefore, at least two of the required elements of the presently claimed invention are absent from Leppla *et al.*

Noteborn *et al.* is cited as disclosing an immunoconjugate containing a viral protein. Noteborn *et al.*, however, does not disclose delivery of an exogenous viral antigen to a cell for processing via the MHC class I pathway and presentation by MHC class I molecules to CTLs (*see*, Declaration ¶9). Noteborn *et al.* teaches methods for delivery of a crude cellular extract containing a chicken anemia viral ("CAV") protein to induce MHC ***class II***-mediated antibody response specific for the CAV protein (*see*, Declaration ¶9). Noteborn *et al.* also teaches delivery of a cytotoxic CAV protein to a cell to deliver the cytotoxic effect (*i.e.*, apoptotic effect) of the ***native*** protein to the cell, but ***not*** an MHC ***class I***-mediated CTL response specific for the CAV protein (*see*, Declaration ¶ 9). There is no disclosure in Noteborn *et al.* of anthrax toxin fusion proteins: (1) comprising a ***full-length protein*** (*i.e.*, a viral protein) bound to a APABP; and (2) an amount sufficient to elicit an MHC class I-mediated CTL response specific for the viral protein. Therefore, at least two of the required elements of the presently claimed invention are absent from Noteborn *et al.*

Since neither Leppla *et al.* nor Noteborn *et al.* teach anthrax toxin fusion proteins: (1) comprising a ***full-length protein*** (*i.e.*, a viral protein) bound to a APABP; and (2) an amount sufficient to elicit an MHC ***class I***-mediated CTL response specific for the viral protein, the references alone and in combination do not contain all of the elements of the presently claimed anthrax toxin fusion proteins.

One of skill in the art would have no motivation to combine the disclosure of Leppla et al. with the disclosure of Noteborn et al. to make the presently claimed compositions

As clearly set forth in the instant specification and in Dr. Leppla's Declaration, delivery of a full length viral protein to a target cell using the presently claimed compositions would lead to processing and presentation of the viral protein by the target cell and subsequent generation of an MHC class I-mediated cytotoxic T cell response specific for the viral protein (*see*, page 2, line 17 to page 3, line 11 and Declaration ¶10). However, delivery of the viral protein would neither kill the target cell as disclosed in Leppla *et al.* and Noteborn *et al.* nor generate a class II-mediated antibody response against the viral protein as disclosed in Noteborn *et al.* (*see*, Declaration ¶10). Thus, one of skill in the art would not be motivated to modify the compositions of Leppla *et al.* or Noteborn *et al.* Moreover, modification of the compositions disclosed by Leppla *et al.* and Noteborn *et al.* to deliver viral proteins to a target cell would render the Leppla *et al.* and Noteborn *et al.* compositions unsuitable for their intended purposes. As explained above, the Federal Circuit has ruled that to establish a *prima facie* case of obviousness, modification of a prior art reference cannot render the prior art unsuitable for its intended purpose (*see*, MPEP §2143.01, citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)).

One of skill in the art would have no reasonable expectation of success in generating the presently claimed compositions by modifying the disclosures of Leppla et al. and Noteborn et al.

As explained above and in ¶¶ 3 and 7 of Dr. Leppla's Declaration, prior to the disclosure of the instant application, one of skill in the art would not have expected that an exogenously introduced full length protein could be processed and presented via the cytosolic MHC class I pathway. Indeed, Noteborn *et al.* confirms the state of the art by disclosing that an MHC ***class II***-mediated antibody response is induced following exogenous delivery of a CAV protein to a cell (*see*, Declaration ¶10). Therefore, one of skill in the art would not expect that modifying the disclosures of Leppla *et al.* and Noteborn *et al.* would lead to the presently claimed anthrax toxin fusion proteins for exogenously delivering full length viral proteins to the cytosolic MHC ***class I*** pathway for processing of the viral protein into epitopes for presentation by MHC class I molecules to CTLs.

No prima facie case of obviousness has been established

As discussed in detail above, the combination of Leppla *et al.* and Noteborn *et al.* does not contain all of the elements of the presently claimed anthrax toxin fusion proteins comprising a full length viral protein bound to APABP and an amount sufficient to elicit an MHC class I-mediated CTL response specific for the viral protein. Moreover, the teachings of Leppla *et al.* in view of Noteborn *et al.* do ***not*** provide one of skill in the art with motivation to practice the claimed invention, nor a reasonable expectation of success for one of skill in the art in practicing the claimed invention. Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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